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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/740,266	12/18/2003	Christian Auclair	1417-03	2270
35811 7590 08/21/2007 IP GROUP OF DLA PIPER US LLP ONE LIBERTY PLACE 1650 MARKET ST, SUITE 4900 PHILADELPHIA, PA 19103			EXAMINER FETTEROLF, BRANDON J	
			ART UNIT 1642	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

**Advisory Action
Before the Filing of an Appeal Brief**

Application No.

10/740,266

Applicant(s)

AUCLAIR ET AL.

Examiner

Brandon J. Fetterolf, PhD

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 August 2007 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:

- a) ☒ The period for reply expires 5 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
(a) ☒ They raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ They raise the issue of new matter (see NOTE below);
(c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☒ They present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).

4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☒ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
The status of the claim(s) is (or will be) as follows:
Claim(s) allowed: _____.
Claim(s) objected to: _____.
Claim(s) rejected: 43-47 and 50.
Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☒ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing of a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08) Paper No(s). _____.
13. ☐ Other: _____.

DETAILED ACTION

Response to the Amendment

The Amendment filed on 8/09/2007 in response to the previous Final Office Action (3/22/2007) is acknowledged, but has not been entered. The instant amendment has not been entered because it introduces new claims 51-54 which do not appear to limit the independent claims from which they depend. As such, they raise new issues that would require further consideration and do not appear to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

Claims 43-47 and 50 are currently under consideration.

The Declarations under 37 CFR 1.132 filed Michel Jean Robert Perricaudet and Celine Bouquet filed after the final action, but before the date of filing a Notice of Appeal will not be entered because Applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not present earlier. For example, the issues, e.g., gene therapy, involved in the rejection under 112 1st paragraph, enablement, for which the Declarations attempt have been previously presented in the Non-Final Office Action of 5/09/2006 and addressed again in the Final Rejection of 3/22/2007.

Rejections Maintained:

All rejections have been maintained because Applicant's arguments appear to be solely drawn to the currently amended claims which have not been entered, as well as the Declaration's submitted after the final action which have not been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

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Claims 43-47 and 50 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. THIS IS A NEW MATTER REJECTION.

Claim 43 has been amended to include the limitation of "a composition consisting essentially of an active agent". While the claims, as originally filed, recites a pharmaceutical composition comprising an active agent, a careful review of the specification and claims, as originally filed, does not appear to lend support for the limitation of "consisting essentially of". In the instant case, it is unclear which elements are excluded from the transitional phrase "consisting essentially of" in claim 43. There is no clear definition provided in the specification for ingredients or steps that would materially affect the composition or the method. See *PPG*, 156 F.3d at 1355, 48 USPQ 2d at 1355 for example. Therefore, the "consisting essentially of" language in the claim is being interpreted as "comprising", see the MPEP § 2111.03. Applicant is invited to point to clear support or specific examples of the claimed limitation in the specification as-filed or remove such amendatory language in response to this action.

Claims 43-47 and 50 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether undue experimentation is required are summarized in *re Wands* 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in *Wands* states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining

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whether undue experimentation is required include: (1) the nature of the invention, (2) the relative skill of those in the art, (3) the breadth of the claims, (4) the amount or direction or guidance presented, (5) the presence or absence of working examples, (6) the quantity of experimentation necessary, (7) the state of the prior art, and (8) the predictability or unpredictability of the art.

Although the quantity of experimentation alone is not dispositive in a determination of whether the required experimentation is undue, this factor does play a central role. For example, a very limited quantity of experimentation may be undue in a fledgling art that is unpredictable where no guidance or working examples are provided in the specification and prior art, whereas the same amount of experimentation may not be undue when viewed in light of some guidance or a working example or the experimentation required is in a predictable established art. Conversely, a large quantity of experimentation would require a correspondingly greater quantum of guidance, predictability and skill in the art to overcome classification as undue experimentation. In *Wands*, the determination that undue experimentation was not required to make the claimed invention was based primarily on the nature of the art, and the probability that the required experimentation would result in successfully obtaining the claimed invention. (*Wands*, 8 USPQ2d 1406) Thus, a combination of factors which, when viewed together, would provide an artisan of ordinary skill in the art with an expectation of successfully obtaining the claimed invention with additional experimentation would preclude the classification of that experimentation as undue. A combination of *Wands* factors, which provide a very low likelihood of successfully obtaining the claimed invention with additional experimentation, however, would render the additional experimentation undue.

The nature of the invention

The claims encompass a method of treating a particular tumor comprising administering a therapeutically effective amount of a composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene. The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." *Mycogen Plant Sci., Inc. v. Monsanto Co.*, 243 F.3d 1316, 1330 (Fed. Cir. 2001).

Level of skill in the art

The level of skill in the art is deemed to be high, generally that of a PhD or MD.

The breadth of the claims

Applicants broadly claim a method of treating or preventing hepatocarcinomas, mesenchymal tumors, neuroectodermal cancer, Ewing's sarcoma and malignant hemopathies associated with chromosomal anomalies comprising administering a therapeutically effective amount of a composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. Thus, the claims encompass method of preventing or treating cancer using gene therapy.

Quantity of experimentation

The quantity of experimentation in the areas of gene therapy for cancer and cancer prevention is extremely large given the unpredictability associated with treating a disease by a method of gene therapy, the lack of correlation of in vitro findings to in vivo success, and the fact that no known cure or preventive regimen is currently available for cancer.

Guidance in the specification and/or Presence of working examples

The specification teaches that pharmaceutical compositions for the treatment or prevention of tumoral pathology comprise an active agent which stabilizes the actin network of the cytoskeleton of a cell, wherein the agent includes, but is not limited to, a zyxin protein, a nucleic acid molecule comprising or constituted of the zyxin gene, a fragment thereof or their complementary sequence, or an antisense nucleic acid thereof, a cell or a set of cells over expressing the zyxin gene or a protein coded for a fragment thereof or an inhibitor of cofilin (page 9, paragraph 0036). The specification further teaches a pharmacological approach for the treatment of cancers by stabilization of the actin network, wherein NIH3T3 and EWS-Fli cells were contacted with dolastin 11 or jasplakinolide and the polymerization of actin was measured by fluorescence (page 30, paragraph 0108-0110). Moreover, the specification provides examples showing that expression of zyxin EWS-FLI cell lines reduce the tumorigenicity of the tumor cells in nude mice (paragraph 0099, Table 1). However, the

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specification appears to be silent on the in-vivo efficacy of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. The specification does not show any success in treating a disease by using a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence. The specification does not contain any teachings that address the ability of the composition to treat a human subject or even its ability to work *in vivo*. Specifically, the specification has not taught an appropriate tested dose for humans, the amount of a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence necessary for successful treatment, the number of cells to be treated, the number of times the treatment needs to be administered or the most appropriate route of administration. Therefore, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are drawn to a pharmaceutical composition comprising a nucleic acid molecule comprising cDNA of a zyxin gene, a fragment thereof or a complementary sequence, and applicant has not enabled the pharmaceutical composition because it has not been shown that these polynucleotides are capable of functioning as to that which is being disclosed. Therefore, coupled with the unpredictability associated with using polynucleotides for the treatment or prevention of cancer, as underscored by the prior art below, the criticality of providing workable examples in an unpredictable art, such as gene therapy and/or cancer therapy, is required for the practice of the instant invention.

The unpredictability of the art and the state of the prior art

The state of the art at the time of filing was such that one of skill could recognize the unpredictability of treating a disease by a method of gene therapy. Gene therapy using administration of recombinant nucleic acids involving *in vivo* or *ex vivo* methods had not seen any success despite a great deal of work and resources. Several reviews in the art show that difficulties with vector selection, mode of delivery and persistence of predictable and effective levels of expression of the protein, created technical barriers to the practice of gene therapy methods. Verma et al states that, “[t]he Achilles heel of gene therapy is gene delivery...”, and that, “most of the approaches suffer from poor efficiency of delivery and transient expression of the gene” (Verma et al. (1997) Nature Volume 389, page 239, column 3, paragraph 2, *of record*). Marshall concurs, stating that, “difficulties in getting genes transferred efficiently to target cells- and getting them expressed-

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remain a nagging problem for the entire field”, and that “many problems must be solved before gene therapy will be useful for more than the rare application” (Marshall (1995) Science, Volume 269, page 1054, column 3, paragraph 2, and page 1055, column 1, *of record*). Numerous factors complicate the gene therapy art which have not been shown to be overcome by routine experimentation. Eck et al. (Goodman & Gilman’s The Pharmacological Basis of Therapeutics (1996), 9th Edition, Chapter 5, McGraw-Hill, NY, *of record*) explains, “the delivery of exogenous DNA and its processing by target cells requires the introduction of new pharmacokinetic paradigms beyond those that describe the conventional medicines in use today”. Eck et al teaches that with *in vivo* gene transfer, one must account for the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein’s compartmentalization within the cell or its secretory fat, once produced. These factors differ dramatically based on the vector used, the protein being produced and the disease being treated (see Eck et al, bridging pages 81-82). Also among the many factors that the art teaches affect efficient gene delivery and sustained gene expression are, immune responses and the identity of the promoter used to drive gene expression. Verma et al teaches, in reference to *ex vivo* methods, that weak promoters produce only low levels of therapeutically effective protein, and that only by using appropriate enhancer-promoter combinations can sustained levels of therapeutically effective protein be achieved (Verma et al, *supra*, page 240, column 2). Verma et al further warns that, “...the search for such combinations is a case of trial error for a given cell type” (Verma et al, *supra*, page 240, bridging sentence of columns 2-3). The state of the art is such that no correlation exists between successful expression of a gene and a therapeutic result (Ross et al, Human Gene Therapy, 1996, Volume 7, pages 1781-1790, *of record*, see page 1789, column 1, first paragraph). Thus, the art at the time of filing clearly establishes that expectation for achieving a desired therapeutic effect *in vivo* by expressing a therapeutic gene using any of the expression constructs known in the art was extremely low. More recently, Rubanyi (Mol. Aspects Med. (2001) 22:113-142, *of record*) teaches that the problems described above remain unresolved. Rubanyi states, “[a]lthough theoretical advantages of [human gene therapy] are undisputable, so far [human gene therapy] has

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not delivered the promised results: convincing clinical efficacy could not be demonstrated yet in most of the trials conducted so far...” (page 113, paragraph 1). Among the technical hurdles that Rubanyi teaches remain to be overcome are problems with gene delivery vectors and improvement in gene expression control systems (see “3. Technical hurdles to be overcome in the future”, beginning on page 116 and continued through page 125). Furthermore, Juengst (British Medical Journal (2003) Volume 326, pages 1410-1411, *of record*) teaches the unpredictable nature of gene therapy and that a few of the apparent successes actually developed T cell-acute lymphoblastic leukemia due to insertional mutagenesis at or near the LMO-2 gene causing altered gene expression. The art has demonstrated that a large amount of experimentation has already been performed without demonstrating successful gene therapy methods for treatment of disease.

With regards to preventing cancer, those of skill in the art recognize that reasonable guidance with respect to preventing any cancer relies on quantitative analysis from defined populations which have been successfully pre-screened and are predisposed to particular types of cancer. This type of data might be derived from widespread genetic analysis, cancer clusters, or family histories. The essential element towards the validation of a preventive therapeutic is the ability to test the drug on subjects monitored in advance of clinical cancer and *link* those results with subsequent histological confirmation of the presence or absence of disease. This irrefutable link between antecedent drug and subsequent knowledge of the prevention of the disease is the essence of a valid preventive agent. Further, a preventive administration also must assume that the therapeutic will be safe and tolerable for anyone susceptible to the disease. Further, treatment of cancer in general is at most unpredictable, as underscored by Gura (Science, v278, 1997, pp.1041-1042) who discusses the potential shortcomings of potential anti-cancer agents including extrapolating from in-vitro to in-vivo protocols, the problems of drug testing in knockout mice, and problems associated with clonogenic assays. Indeed, since formal screening began in 1955, thousands of drugs have shown activity in either cell or animal models, but only 39 that are used exclusively for chemotherapy, as opposed to supportive care, have won approval from the FDA (page 1041, 1st column) wherein the fundamental problem in drug discovery for cancer is that the model systems are not predictive.

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Conclusion

Thus given the broad claims in an art whose nature is identified as unpredictable, the unpredictability of that art, the large quantity of research required to define these unpredictable variables, the lack of guidance provided in the specification, the presence of a working example which does not address the issue of the efficacy of the control and the negative teachings in the prior art balanced only against the high skill level in the art, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as written.

Therefore, No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J. Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 7:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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